REMARKS

Claim amendments

Claims 1, 5, 18, 21 and 22 have been amended to delete the phrase "a derivative of Sag" and Claims 1, 5 and 18 have been amended to delete the term "optionally". In addition, Claims 1, 5 and 18 have been amended to clarify that the vector comprises a therapeutic peptide.

Claim 8 has been amended to recite a method of amplifying B- or T-cells comprising introducing a recombinant vector according to Claim 1 into B- or T-cells under conditions in which the peptide with Sag activity is expressed in the cells. Support for the amendment can be found, for example, on page 9, line 25 through page 10, line 4.

No new matter has been added

Title

The Examiner states that the "title of the invention is not descriptive" (Office Action, page 2).

The title has amended to read: Vectors that Amplify B- or T- Cells

Rejection of Claim 8 under 35 U.S.C. §101

The Examiner rejects Claim 8 under 35 U.S.C. §101 "because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process" (Office Action, page 2).

Claim 8 has been amended to read a method of amplifying B- or T-cells comprising introducing a recombinant vector according to Claim 1 into B- or T-cells under conditions in which the peptide with Sag activity is expressed in the cells, thereby amplifying the B- or T-cells, thereby obviating the rejection.

Rejection of Claims 1-8 and 18-22 under 35 U.S.C. §112, second paragraph

Claims 1-8 and 18-22 are rejected under 35 U.S.C. §112, second paragraph "as being indefinite for failing to particularly point out and distinctly claim the subject matter applicant regards as the invention" (Office Action, page 3).

The Examiner states that in Claims 1, 5 and 18 it is unclear whether a "derivative of the peptide with Sag activity" also has Sag activity or not and that the definition on page 10, lines 18-26 of the specification "does not define the metes and bounds of which structural components are required for Sag activity" (Office Action, page 3).

The phrase "a derivative of the peptide with Sag activity" has been deleted from Claims 1, 5 and 18, thereby obviating the rejection.

The Examiner states that Claim 8 "is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced" (Office Action, page 3).

Claim 8 has been amended to read a method of amplifying B- or T-cells comprising introducing a recombinant vector according to Claim 1 into B- or T-cells under conditions in which the peptide with Sag activity is expressed in the cells.

The Examiner states that in Claims 21 and 22 "it cannot be determined what a derivative of a retroviral vector is" (Office Action, page 3).

The phrase "a derivative of the peptide with Sag activity" has been deleted from Claims 21 and 22.

Applicants' claims, particularly as amended, are definite and particularly point out the subject matter which Applicants regard as the invention.

Rejection of Claims 1-8 and 18-22 under 35 U.S.C. §112, first paragraph

Claims 1-8 and 18-22 are rejected under 35 U.S.C. §112, first paragraph "as failing to comply with the written description requirement" (Office Action, page 4). The Examiner states that the "claims do not require that the Sag derivatives or the derivative of the retroviral vector possess any particular distinguishing feature, biologic activity, or conserved structure" (Office Action, page 4).

The phrase "a derivative of the peptide with Sag activity" has been deleted from the claims, thereby obviating the rejection.

Rejection of Claims 1-4 under 35 U.S.C. §102(a)

Claims 1-4 are rejected under 35 U.S.C. §102(a) "as being anticipated by Lapeyre et al. (WO 95/00178)" (Office Action, page 5). The Examiner states that Lapeyre *et al.* "claim a DNA

comprising a superantigen under the control of a promoter that is capable of expression in a mammalian cell" and that the "DNA is a recombinant vector, a plasmid[,] a viral vector, a retroviral vector or an adeno-associated virus" (Office Action, page 6).

As amended, Applicants' claimed invention is directed to a retroviral vector comprising, in operable linkage, a) a nucleotide sequence of or corresponding to at least a portion of a vector, which portion is capable of infecting and directing the expression of a coding sequence in target cells; and b) one or more coding sequences wherein at least one sequence encodes a peptide with Sag activity; and c) at least one sequence encoding a peptide selected from the group consisting of: a therapeutic peptide and a non-therapeutic peptide.

In contrast, Lapeyre *et al.* teach "a superantigen encoding gene cassette positioned under control of a promoter element expressible in a mammalian cell, the gene and promoter being adapted for expression in a eukaryotic cell" (Lapeyre *et al.*, Claim 1). Lapeyre *et al.* do not teach addition of a therapeutic gene to the superantigen encoding gene cassette.

Thus, Lapeyre *et al.* do not anticipate Applicants' claimed invention, particularly as amended.

Rejection of Claims 1-8 and 18-22 under 35 U.S.C. §103(a)

Claims 1-8 and 18-22 are rejected under 35 U.S.C. §103(a) "as being unpatentable over Gunzburg et al. . . . and Gilboa" (Office Action, page 6). The Examiner states that Gunzburg "identify a promoter located in the U3 region of the 5' MMTV LTR and splice donor/acceptor sites expressing an endogenous superantigen (Sag)" and that "superantigen expression results in T-cell proliferation" (Office Action, page 7). The Examiner cites Gilboa *et al.* as teaching a "murine retroviral vector comprising a 5' LTR and a completely or partially deleted U3 region of the 3' LTR replaced by a heterologous promoter and a DNA sequence followed by R-U5" and a host cell complementing elements that are missing in the recombinant vector deficient in viral replication" (Office Action, page 7). It is the Examiner's opinion that:

> One of ordinary skill in the art at the time the invention was made would have been motivated to replace at least a portion of the 3' LTR U3 region with a heterologous promoter and DNA sequence, taught by Gilboa, into the MMTV of Gunzburg et al. to generate self-inactivating vectors. The proviral DNA from

> these vectors are transcriptionally inactive, which results in the expression of the heterologous insert. One of ordinary skill in the art would also have been motivated to delete at least a portion of the 3' LTR U3 region within the MMTV of Gunzburg et al. to disable activation of cellular oncogenes . . . One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of producing an MMTV expressing Sag and 3' LTR U3 region comprising a heterologous promoter and DNA sequence because Gunzburg et al. specifically identify the nucleotides and splice sites required for Sag expression and Gilboa teach that self-inactivating vectors are generated by deleting or replacing any portion of the 3' LTR U3 region. Therefore, the segments required for expression of Sag, taught by Gunzburg et al., and the mutations within the 3' LTR U3 region, taught by Gilboa do not overlap. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art, absent unexpected results to the contrary (Office Action, pages 7-8).

Applicants respectfully disagree. An obviousness rejection requires both (1) that "the prior art would have suggested to the person of ordinary skill in the art that they should . . . carry out the claimed process"; and (2) that the prior art should establish a reasonable expectation of success. *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). "Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in applicant's disclosure." *Id.*

Neither Gunzburg *et al.* nor Gilboa teaches a recombinant vector comprising a Sag gene and a therapeutic gene. In addition, neither Gunzburg *et al.* nor Gilboa teaches a recombinant retroviral vector which is capable of undergoing ***promoter conversion*** and is replication-defective, and comprises a completely or partially deleted ***U3 region that is replaced by a promoter which directs expression of a DNA sequence in the body of the retroviral vector***. As amended, Claim 5 clearly recites a vector which comprises in operable linkage a) a 5' LTR comprising the structure U3-R-U5 ***followed by***, b) one or more coding sequences wherein at least one of sequence encodes a peptide with Sag activity, ***followed by*** c) a 3' LTR comprising a completely or partially deleted U3 region which comprises heterologous DNA that includes regulatory elements that regulate expression of the coding sequences. Thus, in Applicants' claimed retroviral vector, the promoter is in the 5' LTR and the coding sequence is in the body of the vector. Applicants teach in the specification:

According to the procon principle a retroviral vector is constructed in which the right hand U3 region is altered (Figure 7), but the normal left hand U3 structure is maintained (Figure 7); the vector can be normally transcribed into RNA utilizing the normal retroviral promoter located within the left hand U3 region (Figure 7). However, the generated RNA will only contain the altered right hand U3 structure. In the infected target cell, after reverse transcription, this altered U3 structure will be placed at both ends of the retroviral structure (Figure 7).

If the altered region carries a polylinker (see below) instead of the U3 region then ***any promoter***, including those directing tissue specific expression (see below) can be easily inserted. This ***promoter will then be utilized exclusively in the target cell for expression of linked genes carried by the retroviral vector***. Alternatively or additionally DNA segments homologous to one or more cellular sequences can be inserted into the polylinker for the purposes of gene targeting.

In the packaging cell line the expression of the retroviral vector is regulated by the normal unselective retroviral promoter (Figure 7). However, as soon as the vector enters the target cell promoter conversion occurs, and the therapeutic genes are expressed from a tissue specific promoter of choice introduced into the polylinker (Figure 7). Not only can virtually any tissue specific promoter be included in the system, providing for the selective targeting of a wide variety of different cell types, but additionally, following the conversion event, the structure and properties of the retroviral vector no longer resembles that of a virus (specification, page 6, line14 - page 7, line 5).

Gunzburg *et al.* teach that a "novel U3 promoter (^{MMTV}P2) directs Sag expression in B cells" and that the promoter is "able to direct efficient Sag activity in the absence of the previously described MMTV promoter" (Gunzburg *et al.*, page 158, column 1). ***Gunzburg e al. do not teach expression of the Sag gene in combination with a therapeutic gene.*** The Examiner notes that Gunzburg *et al.* also do not teach "a replication-defective retrovirus comprising a completely or partially deleted U3 region that is replaced by a promoter expressing heterologous DNA sequences followed by R-U5 or a host cell comprising the retroviral construct", and thus, cites the Gilboa patent (Office Action, page 7).

Gilboa teaches a double copy (DC) vector in which ***a gene directly linked to a promoter is inserted into the U3 region*** of a retrovirus (*e.g.*, the human ADA minigene which "consists of the ADA promoter . . . and the ADA coding sequences", Gilboa, column 11, lines 2-5). Specifically, Gilboa discloses a retroviral vector comprising a 5' LTR, a 3' LTR and a

transcription unit inserted only into the U3' region of the 3' LTR, wherein the transcription unit comprises a promoter and a DNA sequence capable of being transcribed into RNA under the control of the promoter . . . (Gilbóa, column 20, Claim 1). Gilboa does not teach a recombinant retroviral vector which is capable of undergoing ***promoter conversion*** and is replication-defective, and comprises a completely or partially deleted ***U3 region that is replaced by a promoter which directs expression of a DNA sequence in the body of the retroviral vector***. Indeed, Gilboa's DC vectors were designed to avoid placing the gene to be expressed in the body of the vector, and thus, Gilboa teaches away from the use of Applicants' claimed invention. Gilboa states that:

> in all retroviral vectors constructed so far, the transduced gene, i.e., the gene whose expression in the eucaryotic cell is sought, is always placed in between the two LTRs and, therefore, its position relative to the two LTRs will not change in the infected cell. The ***unique feature*** of DC vectors . . . is that the transduced gene is placed within the U3 region of the 3' LTR . . . [and] that in an infected cell the gene is transferred also to the 5' LTR, generating two copies of the transduced gene, hence its name, double copy vector. The ***important result*** is that in its new position, in the 5' LTR, the gene is physically placed outside the retroviral transcriptional unit, eliminating or at least reducing the negative effects of the retroviral transcriptional unit (Gilboa, column 10, lines 47-61, emphasis added).

In Applicants' claimed promoter conversion retroviral vector, the transduced gene is not placed within the U3 region of the 3' LTR and the vector does not generate two copies of the transduced gene.

Based on the teachings in the Gilboa patent one of skill in the art would not be motivated to express the Sag gene in Applicants' claimed ProCon vector. Nevertheless, even if one of skill in the art were to use the ProCon vector to express the Sag gene, the cited art clearly does not mention or even suggest combining the Sag with a therapeutic gene for any purpose.

The combined teaching of Gunzburg *et al.* and Gilboa clearly do not render obvious Applicants' claimed invention, particularly as amended.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Anne J. Collins

Anne J. Collins
Registration No. 40,564
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

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